U.PORTO
INSTITUTO DE CIÊNCIAS BIOMÉDICAS ABEL SALAZAR
UNIVERSIDADE DO PORTO

Dissertação: Artigo de Revisão Bibliográfica

Mestrado Integrado em Medicina

THE LINK BETWEEN AUTOIMMUNE AND ALLERGIC DISEASES: A SYSTEMATIC REVIEW

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Porto 2017

ABSTRACT

Introduction: Autoimmune diseases are caused by the loss of immunologic tolerance to self-antigens, causing the formation of autoantibodies, which mistakenly attack the body. Allergic diseases are also common causes of chronic illnesses contributing to rising health costs. Actually, the term “allergy” is frequently used synonymously with IgE-mediated allergic disease. Some authors considered that these diseases are at opposite sides of the spectrum of the immune response because autoimmune and allergic diseases are considered T helper 1- and T helper 2-mediated diseases, respectively. However, despite these diseases have different clinical manifestations, there has been an increasing evidence of association between them.

Objectives: The proposed study aimed at systematically review the link between autoimmune and allergic diseases: to investigate the etiology, pathophysiology and risk factors in order to clarify the relationship among the two groups.

Development: This work was carried out by searching data on Pubmed using the keywords "autoimmune diseases”, “autoimmunity”, "allergic", “allergy”, “atopy”. Some authors reported a link between allergic rhinitis, asthma and systemic lupus erythematous as well as a relationship between autoimmune thyroid diseases and additional autoimmune/allergic diseases. In fact, both allergic and autoimmune diseases are manifestations of immunological hypersensitivity that arise when controlling mechanisms to innocuous environmental or endogenous antigens break down. Although there is an increasing evidence of a relationship between some allergic and autoimmune diseases, there is a lack of information in what concerns the pathophysiological mechanisms that explain it.

Conclusions: Based on the findings of this review, given the increasing evidence of a relationship between autoimmune and allergic diseases and the lack of knowledge in what concerns the overlap of their pathophysiologic mechanisms, future research should focus on identifying the basic mechanism of this relationship.

KEYWORDS: autoimmune diseases; autoimmunity; allergic; allergy; atopy

RESUMO

Introdução: As doenças autoimunes são causadas pela perda de tolerância imunológica aos autoantigénios, levando à formação de autoanticorpos, que atacam o organismo por engano. As doenças alérgicas também são uma causa comum de doenças crónicas contribuindo para o aumento dos custos em saúde. Na verdade, o termo "alergia" é frequentemente utilizado como sinónimo de doença alérgica medidada por IgE. Alguns autores consideraram que estas doenças estão em lados opostos do espectro da resposta imunológica, porque as doenças autoimunes e alérgicas são consideradas doenças mediadas por células Th1 e Th2, respetivamente. No entanto, apesar destas doenças terem manifestações clínicas diferentes, tem havido uma evidência crescente da associação entre elas.

Objetivos: O estudo proposto pretendeu rever sistematicamente a relação entre doenças autoimunes e alérgicas: investigar a etiologia, fisiopatologia e fatores de risco para esclarecer a relação entre os dois grupos.

Desenvolvimento: Este trabalho foi realizado através da pesquisa de dados no Pubmed usando as palavras-chave "doenças autoimunes", "autoimunidade", "alérgica", "alergia", "atopia". Alguns autores descreveram uma ligação entre rinite alérgica, asma e lúpus eritematoso sistémico, assim como uma relação entre doenças autoimunes da tiróide e doenças autoimunes/alérgicas adicionais. De facto, tanto as doenças alérgicas como as autoimunes são manifestações de hipersensibilidade imunológica que surgem quando há uma desregulação dos mecanismos de controlo de antigénios ambientais ou endógenos. Apesar de haver uma evidência crescente da relação entre algumas doenças alérgicas e as doenças autoimunes, existe ainda falta de informação no que diz respeito aos mecanismos fisiopatológicos que a explicam.

Conclusões: Com base nos resultados desta revisão, dado a crescente evidência de uma relação entre doenças autoimunes e alérgicas e a falta de conhecimento sobre a sobreposição de seus mecanismos fisiopatológicos, no futuro, a investigação deverá concentrar-se na identificação do mecanismo básico dessa relação.

PALAVRAS-CHAVE: doenças autoimunes; autoimunidade; alérgicas; alergia; atopia

ACKNOWLEDGEMENTS

At the end of another academic phase, I would like to thank all those who help me on this journey.

My acknowledgments go to Instituto de Ciências Biomédicas Abel Salazar and to the University of Porto.

I would like to thank Dr. Cristiana Almeida for accepting to guide this work. I would like also to express her my gratitude for providing me always guidance and prompt help.

I would like to thank Prof. Doctor Isabel Almeida for her support, valuable help and the good guidance throughout this work.

Finally, my very special thanks to my family, in particular to my parents, for their constant love and support throughout my life, my husband and my daughter, who always stands by me all the time, and to my dear friends. Thank you for all the support and patience.

ABBREVIATIONS

AID – autoimmune diseases

ANA – antinuclear antibodies

FOXP – forkhead box P

HVEM – herpes virus entry mediator

IFN – interferon

Ig – immunoglobulin

IL – interleukin

IPEX – immunodysregulation polyendocrinopathy enteropathy X-linked

PGM – phosphoglucomutase

SHVEM – soluble herpes virus entry mediator

SoJIA – systemic onset juvenile idiopathic arthritis

TGF – tumour growth factor

Th – T helper

TNFR - tumour necrosis factor receptor

Treg – regulatory T cells

TABLES

CONTENTS

INTRODUCTION

Atopic and autoimmune reactions belong to the group of hypersensitivity reactions of the immune system. They are categorized in different names depending on whether the antigen triggering the reaction is endogenous or exogenous, types of cellular and humoral components involved, and clinical symptoms (Andersen *et al.*, 2017).

Autoimmune diseases (AID) are characterized by the reaction of cells (auto reactive T-lymphocytes) or products (autoantibodies) of the immune system against the organism's own antigens (autoantigens). It may be part of the physiological immune response (natural autoimmunity) or pathologically induced, which may eventually lead to the development of clinical abnormalities – AID. The incidence of AID has increased in recent decades (D'Angelo *et al.*, 2016) and their chronic and debilitating characteristics have become a massive burden on patients, families and society, with high medical costs and reduced quality of life (Zhang *et al.*, 2016).

The AID are classified based on site of involvement and nature of lesion as hemocitolytic, localized (or organ specific) and systemic (or non-organ specific) (McGonagle *et al.*, 2006). Despite the classification, all AID's subtypes usually exhibit an elevated level of immunoglobulins, demonstrable autoantibodies, accumulation of lymphocytes and plasma cells at the sites of lesion, benefit with corticosteroid or other immunosuppressive therapy, the occurrence of more than one type of autoimmune lesion in an individual, a genetic predisposition toward autoimmunity, higher incidence among females and chronicity (usually nonreversible) (Kasper *et al.*, 2015).

Although these conditions have a multifactorial pathogenesis, the generally accepted model is that immune dysregulation, secondary to an infectious process or excessive exposure to an inciting or cross-reactive antigen, promotes a T helper (Th)1 response leading to progressive inflammation and autoimmunity (D'Angelo *et al.*, 2016). These diseases may result from multiple interactions of genes and environmental factors. In fact, even if inherit a genetic predisposition, the AID will not occur unless there is an environmental trigger. In what concerns the genetic factors in autoimmunity, different genes can increase susceptibility to autoimmune diseases including genes encoding histocompatibility molecules, complement proteins, immunoglobulins, peptide transporter proteins, and genes controlling the production of sex hormones. On the other hand, there are also several suspects in the search for triggers such as viruses, bacteria, diet, toxins, radiation, metal, estrogen and chronic infections. Thus, in an individual with a susceptible genotype, exposure to environmental factors can act to initiate an autoimmune process

(Carson, 1992).

Similarly to AID, allergic diseases are very common in developed countries, particularly among children, adolescents and young adults (Żukiewicz-Sobczak *et al.*, 2012). Allergic rhinitis, asthma, and atopic eczema are among the commonest causes of chronic diseases contributing to rising health costs (Kay, 2001). Although the term "allergy" has been introduced in 1906 by von Pirquet, who recognized that in both protective and hypersensitivity reactions, antigens had induced changes in reactivity, the term was corrupted and now is frequently used synonymously with immunoglobulin (Ig) E-mediated allergic disease (Kay, 2001). Thus, atopy is a genetic predisposing factor to produce IgE antibodies in response to low doses of allergens and to develop typical symptoms such as atopic dermatitis, allergic rhinitis and asthma (Johansson *et al.*, 2001; Miraglia Del Giudice *et al.*, 2012). Atopic diseases have increased in frequency in recent decades and now affect approximately 20% of the population worldwide (Spergel, 2010). The risk of developing atopic diseases is complex and is strongly influenced by environmental and genetic factors (Bantz *et al.*, 2014; Spergel, 2010), playing the latter the main role. In what concerns the environmental factors, it was been described factors as infectious agents (human rhinoviruses, respiratory syncytial virus, and mycoplasma), allergens (house dust mites, pollens, pets, and molds), pollutants and medication exposure (Asher *et al.*, 2010; Guilbert *et al.*, 2010; Nishimura *et al.*, 2013).

Allergic diseases are due to an immunological response to a usually innocuous antigen (allergen) resulting in the proliferation of Th2 lymphocytes (Pacheco-Gonzalez *et al.*, 2016).

Some authors considered that these diseases are at opposite sides of the spectrum of the immune response. In fact, as mentioned, AID, such as multiple sclerosis, rheumatoid arthritis and type 1 insulin-dependent diabetes mellitus, are considered Th1-mediated diseases, while allergic disorders, such as asthma, food allergy or rhinitis, are considered to be Th2-mediated diseases (Pedotti *et al.*, 2003). However, despite these diseases have different clinical manifestations, there has been an increasing evidence of association between allergic conditions and AID in the last years (Larche *et al.*, 2005). As an example, some authors reported a link between several allergic disorders such as allergic rhinitis or asthma and systemic lupus erythematous (Morton *et al.*, 1998; Sekigawa *et al.*, 2003; Sin *et al.*, 2016). In fact, both allergic and AID are manifestations of immunological hypersensitivity that arise when mechanisms controlling responses to innocuous environmental antigens (such as allergens) or to endogenous host ('self') proteins, break down (Dagdelen *et al.*, 2012). The reason of certain individuals suffer from

particular hypersensitivities is unclear, however there is evidence that both genetic and environmental factors influence their susceptibility (Larche *et al.*, 2005).

Although there is an increasing evidence of a relationship between some allergic and AID, there is a lack of a systematic review that identify the most prevalent associations as well as the current pathophysiological mechanisms that explain it. Thus, the authors decide to make a literature review that summarizes what was studied in last fifteen years regarding the connection between atopy and AID. The proposed study aims to systematically review the link between autoimmune and allergic diseases: to investigate the etiology, pathophysiology and risk factors of allergic and AID in order to clarify the relationship between the two groups.

METHODS

Search strategy

We conducted a systematic review about the link between autoimmune and allergic diseases. The search was conducted on March 7, 2017 using PubMed database with the keywords “autoimmune diseases” or “autoimmunity” in conjunction (or not) with “allergic”, “allergy” or “atopy”. The search was restricted to original paper researches published in the last fifteen years (after January 1, 2002) in the english language. The results of search included a total of 38 992 articles.

Article selection

All titles were screened for keywords related to autoimmune and allergic diseases. All review were removed, reminding 30 086 papers. The papers tittles were analyzed and, after non-related and duplicates removal, remained 57 articles selected. In the next step, all abstracts were reviewed by one author (Certal M) and a final decision on their inclusion in or exclusion from this review was made based on the following criteria: (1) being an original paper research (reviews were excluded); (2) published in the english language; (3) published after January 1, 2002 and before March 7, 2017; (4) includes a correlation between autoimmune and allergic diseases in the title. Of 57 full text screened, 28 publications were included in this review.

Introduction, discussion and review papers provided background to our systematic review but were not included in the data extraction form, as they did not provide primary data.

DEVELOPMENT

The link between autoimmune and allergic diseases

The widely-debated link between allergic diseases and autoimmunity aims to establish, in the most recent studies, if the autoreactivity can represent a simple epiphenomenon of the chronic inflammation or whether it is the key element in the development of allergic diseases or whether allergic diseases are associated with the development of autoimmunity.

Despite the relationship between autoimmune and allergic diseases remain controversial, in the past fifteen years, more groups reported a link between them. This link exists in respect to the epidemiology, etiology, risk factors, as well as, pathophysiology.

Epidemiology

In what concerns the study of epidemiologic parameters, such as incidence and prevalence of allergic and AID, some epidemiological studies suggested a lower incidence of allergy among patients with AID, including rheumatoid arthritis (Rudwaleit *et al.*, 2002; Verhoef *et al.*, 1998) and multiple sclerosis (Bergamaschi *et al.*, 2009). These data were supported by the counteracting immune mechanisms of these diseases. In fact, as described above, AID are considered Th1/Th17-mediated diseases, while allergic disorders are considered to be Th2-mediated diseases (Pedotti *et al.*, 2003) and these mechanisms may be responsible for the differences in the prevalence of them. However, more recently, despite the different immune mechanisms and clinical manifestations of allergic and AID, there has been an increasing evidence of association between them (table 1) (Kreiner *et al.*, 2017; Larche *et al.*, 2005; Rabin *et al.*, 2008).

Concerning allergic and AID epidemiology data uncovered in the last fifteen years, Dagdelen and collaborators described that patients with autoimmune thyroid diseases (particularly, Hashimoto's thyroiditis and Graves' disease) were prone to additional autoimmune/allergic diseases (Dagdelen *et al.*, 2012). The distribution of these disorders were 10.2% gastrointestinal (chronic atrophic gastritis, celiac disease, autoimmune pancreatitis, ulcerative colitis, primary biliary cirrhosis), 6.6% allergic (asthma, chronic urticaria, rhinosinusitis), 4.4% rheumatological (rheumatoid arthritis, systemic lupus erythematosus, Still disease, Sjögren syndrome, Behçet's disease, ankilosying

spondylitis), 3.7% skin (vitiligo, psoriasis, idiopathic pruritus, total alopecia), 1.5% endocrinological (hypoparathyroidism, type-1 diabetes mellitus, hypophysitis), 0.4% hematological (idiopathic thrombocytopenic purpura), 0.4% renal (crescenteric glomerulonephritis) involvements in Hashimoto's thyroiditis. In Graves' disease, these distributions were similar with 3.8% gastrointestinal, 3.8% allergic, 3.8% skin, 1.9% rheumatological and 1.9% hematological. In this work, the mostly involved organ system described was the gastrointestinal tract in both, that, probably, takes play in exaggeration of some symptoms by leading to anemia caused by both vitamin B12 and iron deficiencies, especially in patients with Hashimoto's thyroiditis (Dagdelen *et al.*, 2012).

Barahmani and collaborators performed a previous study, using National AA Registry database, with the purpose of investigate the association between history of atopy (asthma, atopic dermatitis, and hay fever) or AID (irritable bowel syndrome, psoriasis, and any thyroid disorder) and risk of alopecia areata. The results revealed that processing a history of any atopic or autoimmune disease was associated with an increased risk of alopecia areata. There was no trend for possessing a history of more than one atopic or autoimmune and increasing risk of alopecia areata. This analysis revealed that a history of atopy and autoimmune disease was associated with an increased risk of alopecia areata and that the results were consistent for both the severe subtype of alopecia areata (ie, alopecia totalis and alopecia universalis) and the localized subtype (ie, alopecia areata persistent) (Barahmani *et al.*, 2009).

A population-based case-control study investigated the association between common allergic diseases (allergic conjunctivitis, allergic rhinitis, atopic dermatitis, asthma, and urticaria) and the subsequent risk of developing primary immune thrombocytopenia during childhood (Chiang *et al.*, 2015). In these work, Chiang and collaborators showed that children with every type of allergic disease examined (except asthma) exhibited an increased risk of developing primary immune thrombocytopenia. In addition, in the last year, some authors conducted a population-based cohort analysis and described a significantly increased incidence of primary immune thrombocytopenia in children with atopic dermatitis and showed that children with both atopic dermatitis and primary immune thrombocytopenia had higher occurrence rates of other autoimmune diseases (Wei *et al.*, 2016).

It has been also described a significant association between common allergic diseases, such as asthma and allergic rhinitis, and the incidence of rheumatoid arthritis in a population-based cohort study (Lai *et al.*, 2015). In addition, this study also demonstrated that patients with more than one allergic disease had an increased risk of developing rheumatoid arthritis (Lai *et al.*, 2015).

Recently, Andersen and collaborators also suggested that atopic dermatitis was significantly associated with alopecia areata, vitiligo, chronic urticaria, celiac disease, chronic glomerulonephritis, Sjögren syndrome, systemic lupus erythematous, ankylosing spondylitis, Crohn's disease, unspecified inflammatory bowel disease (patients with concurrent diagnosis of Crohn's disease and ulcerative colitis), ulcerative colitis and rheumatoid arthritis. In this study, atopic dermatitis was also associated with having multiple autoimmune comorbidities and patients with history of smoking had a significantly higher occurrence of them compared to nonsmokers (Andersen *et al.*, 2017).

Lin and collaborators, in 2016, described, in a population-based case-control study, that children with onset of allergic diseases were at increased risk of developing juvenile idiopathic arthritis and the increased risk was associated with the cumulative effect of concurrent allergic diseases and frequency of seeking medical care (Lin *et al.*, 2016).

Another group documented a twofold prevalence of chronic autoimmune thyroiditis in systemic nickel allergic syndrome subjects compared that observed in patients with no-systemic nickel allergic syndrome immune diseases (26.5 vs 12.7 %, $p < 0.01$) (Andrioli *et al.*, 2015). In what concerns the nickel-induced allergy, more studies were performed in order to identify a link between AID's development. Al-Mogairen and collaborators performed an experimental study in Brown Noeway rats that aimed at investigate whether nickels chloride can induce autoimmunity and cutaneous sclerosis in immunosensitive rats. In this work, serum ANA was high in a significant number of rats in both the oral and subcutaneously nickel-treated groups, while the anti-SCL70 was high in a significant number of rats in only the orally nickel-treated group. Histologically, subcutaneous and oral nickel-treated groups showed sclerodermic features of the skin, respectively. This study suggested that nickel chloride can induce scleroderma-related autoantibodies and cutaneous sclerosis, and a more prolonged duration of exposure is probably associated with greater risk (Al-Mogairen *et al.*, 2010).

Yeh and collaborators performed a national population-based study and described an increased subsequent risk of myasthenia gravis in patients with allergic conjunctivitis, allergic rhinitis, Hashimoto thyroiditis, and Graves' disease, suggesting an association between allergic or AID and the risk of myasthenia gravis. In addition, they also described that the highest risk of subsequent myasthenia gravis was associated with combined allergic conjunctivitis and Hashimoto thyroiditis (Yeh *et al.*, 2015).

Finally, although some studies not clearly evidence the link between autoimmune and allergic diseases, they show that these diseases tend to walk side by side. For

example, it was described, in a population-based study, an association between attention deficit hyperactivity disorder and allergic/autoimmune diseases, particularly, asthma, allergic rhinitis, atopic dermatitis, urticaria, ankylosing spondylitis, ulcerative colitis and autoimmune thyroid disease (Chen *et al.*, 2017).

Despite the increasing epidemiologic evidence of a link between autoimmune and allergic diseases, there also have been reported no differences between them. For example, a study performed in adult and pediatric alopecia areata patients demonstrated that the frequencies of autoimmune and atopic diseases were not different between these groups and control group. In addition, they also showed no statistically significance between disease severity and personal or familiar history of AID in the two groups (Serarslan *et al.*, 2012). Another study performed by Alonso and collaborators show controversy results. This group conducted a case-control study in order to assess the association between history of allergy (pollens, house dust, animal dander, foods, drugs allergy and clinical manifestations such as conjunctivitis, rhinitis, asthma or hives) and autoimmune diseases (such as multiple sclerosis, optic neuritis, systemic lupus erythematous, rheumatoid arthritis, hyperthyroidism, and type 1 diabetes), and the risk of multiple sclerosis. In this work, history of allergy was not associated with multiple sclerosis risk and a modest association was found between family history of other AID and multiple sclerosis. Thus, family history of other autoimmune diseases was associated with a higher multiple sclerosis risk, suggesting a common genetic background or shared environmental triggers. There was no clear association between personal history of allergy and risk of multiple sclerosis (Alonso *et al.*, 2008).

Table 2 Epidemiological evidence of association between autoimmune and allergic diseases.

AUTOIMMUNE DISEASE	ALLERGIC DISEASE
Alopecia areata (Andersen *et al.*, 2017)	• Atopic dermatitis (Andersen *et al.*, 2017; Barahmani *et al.*, 2009) • Asthma (Barahmani *et al.*, 2009) • Hay fever (Barahmani *et al.*, 2009)
Ankylosing spondylitis (Andersen *et al.*, 2017)	• Atopic dermatitis (Andersen *et al.*, 2017)
Autoimmune thyroiditis (Andrioli *et al.*, 2015; Dagdelen *et al.*, 2012)	• Asthma (Dagdelen *et al.*, 2012) • Chronic urticaria (Dagdelen *et al.*, 2012) • Rhinosinusitis (Dagdelen *et al.*, 2012) • Systemic nickel allergic syndrome (Andrioli *et al.*, 2015)

Celiac disease (Andersen *et al.*, 2017)	• Atopic dermatitis (Andersen *et al.*, 2017)
Crohn's disease (Andersen *et al.*, 2017)	• Atopic dermatitis (Andersen *et al.*, 2017)
Chronic glomerulonephritis (Andersen *et al.*, 2017)	• Atopic dermatitis (Andersen *et al.*, 2017)
Chronic urticaria (Andersen *et al.*, 2017)	• Atopic dermatitis (Andersen *et al.*, 2017)
Graves' disease (Dagdelen *et al.*, 2012)	• Asthma (Dagdelen *et al.*, 2012) • Chronic urticaria (Dagdelen *et al.*, 2012) • Rhinosinusitis (Dagdelen *et al.*, 2012)
Juvenile idiophatic arthritis (Lin *et al.*, 2016)	• Allergic diseases (Lin *et al.*, 2016)
Myasthenia gravis (Yeh *et al.*, 2015)	• Allergic conjunctivitis (Yeh *et al.*, 2015) • Allergic rhinitis (Yeh *et al.*, 2015)
Primary immune thrombocytopenia (Chiang *et al.*, 2015; Wei *et al.*, 2016)	• Allergic conjunctivitis (Chiang *et al.*, 2015) • Allergic rhinitis (Chiang *et al.*, 2015) • Atopic dermatitis (Chiang *et al.*, 2015; Wei *et al.*, 2016) • Asthma (Chiang *et al.*, 2015) • Urticaria (Chiang *et al.*, 2015)
Reumathoid arthritis (Andersen *et al.*, 2017; Lai *et al.*, 2015)	• Atopic dermatitis (Andersen *et al.*, 2017) • Asthma (Lai *et al.*, 2015) • Allergic rhinitis (Lai *et al.*, 2015)
Sjögren syndrome (Andersen *et al.*, 2017)	• Atopic dermatitis (Andersen *et al.*, 2017)
Systemic lupus erythematous (Andersen *et al.*, 2017)	• Atopic dermatitis (Andersen *et al.*, 2017)
Scleroderma (Al-Mogairen *et al.*, 2010)	• Systemic nickel allergic syndrome (Al-Mogairen *et al.*, 2010)
Vitiligo (Andersen *et al.*, 2017)	• Atopic dermatitis (Andersen *et al.*, 2017)

Finally, some studies appeared that aimed at study not the relation between the AID and the allergic diseases but, rather, the relationship between the applied treatments and the further development of these diseases. Accordingly, Bozek and collaborators performed a 20-year observational evaluation post-specific immunotherapy, a therapy that involves the stimulation of immune tolerance with regard to a particular allergen and that is a recognized treatment for selected allergic diseases, such as allergic rhinitis and conjunctivitis, food allergies or atopic dermatitis (Pitsios *et al.*, 2015). This work was

performed for an assessment of any manifestations of AID or the appearance of autoantibodies in serum of post-specific immunotherapy patients (Bozek *et al.*, 2015). Unlike the other studies, in this work, they didn´t find no significant differences in the AID prevalence between the allergic patients with or without post-specific immunotherapy. However, significantly higher prevalence of 4 different autoimmune diseases were observed in the non-allergic patients during the same period. Additionally, the incidence of 8 different autoantibodies was significantly higher in non-allergic patients than in control subjects. Hashimoto's disease was the most common AID observed. The results of this long-term observational study indicated a lack of a significant prevalence of new instances of AID during 20 years of observation post-specific immunotherapy and at a rate lower than that of non-allergic control subjects, suggesting that specific immunotherapy is safe in this regard in the long term (Bozek *et al.*, 2015).

Etiology

Despite the increasing evidence of a relationship between some allergic and AID, particularly in what concerns the epidemiological data, there is a lack of information about the etiology of both diseases as well as the pathophysiological mechanisms that explain it.

Genetic and environmental factors participate in the pathogenic mechanisms of both autoimmune and allergic diseases (Pacheco-Gonzalez *et al.*, 2016). This observation is in apparent contrast with the understanding of allergy and AID as representatives of distinct immunological disorders with counteracting underlying immune mechanisms (Kreiner *et al.*, 2017).

In what concerns genetic factors or heredity of autoimmune and allergic diseases, it was documented that the occurrence of some autoimmune disorders in parents, especially psoriasis and rheumatoid arthritis/ankylosing spondylitis, significantly increases the occurrence of allergic diseases in their children (Maas *et al.*, 2014).

In fact, genetic factors also have been described as major etiologic factors of autoimmune and allergic diseases, participating in the pathogenic mechanisms of both. Both allergy and AID are highly heritable diseases and an increasing number of susceptibility loci have been discovered. Some studies demonstrated substantial commonalities between them in terms of susceptibility loci, genetic pathways and genomic regulatory sites.

Kreiner and collaborators performed a meta-analysis and described an enrichment of allergy associated loci in 29 among 290 loci previously associated with 16 autoimmune

diseases (Kreiner *et al.*, 2017). Despite some limitations of the study, such as the different clinical phenotypes, with allergic sensitization often being present without symptoms and vice versa, this overlap in genetic mechanisms seemed to be a general phenomenon for allergy or AID, and distinct from other diseases (Kreiner *et al.*, 2017).

Recently, Pacheco-Gonzalez and collaborators also demonstrated, through an observational case-control study, that there are some genetic variants of Forkhead Box P3 (FOXP3), a gene involved in IPEX syndrome (immunodysregulation polyendocrinopathy enteropathy X-linked), also called XLAAD or X-linked autoimmunity-allergic dysregulation (Chatila *et al.*, 2000), that are significantly more frequent in children who share allergic and AID (Pacheco-Gonzalez *et al.*, 2016). In this work, the authors defined 13 different polymorphisms in the FOXP3 gene, seven of which had not been previously described. There was an increase in the presence of the mutated allele in the position 7340C>T, specifically in those patients that suffered from both atopic and autoimmune diseases. This polymorphism is located in the 3' untranslated region, which is described as regulatory region, since it could modify mRNA stability and translation efficiency (Bennett *et al.*, 2001). In addition, this polymorphism could modify cellular localization signals affecting protein location, and consequently, FOXP3 function.

Studying commonalities in the genetic characteristics of both autoimmune and allergic diseases could provide a key to understand the complex relationship between them by pinpointing possible common pathophysiological mechanisms. In fact, this might help to explain the mechanisms and aetiologies responsible for the contemporaneous, dramatic increase in incidence of allergic and AID (Bach, 2002; Kreiner *et al.*, 2017).

Despite the importance of genetic factors in these diseases appearance, environmental factors also contribute to the development of both autoimmune and allergic diseases. However, although it is well documented that both autoimmune and allergic diseases are influenced by environmental factors, there are few studies published in the last fifteen years that demonstrate a clear association between them. In fact, recently, only a cohort study performed by Sevelsted and collaborators, demonstrated that allergy and autoimmune disorders share environmental risk factors including birth by caesarean section (Sevelsted *et al.*, 2015). In this study, the authors demonstrated that children delivered by caesarean had significantly increased risk of asthma, systemic connective tissue disorders, juvenile arthritis, inflammatory bowel disease, immune deficiencies, and leukaemia (Sevelsted *et al.*, 2015).

Pathophysiology

Atopy and autoimmunity are two potential outcomes of dysregulated immunity (D'Angelo *et al.*, 2016; Shah, 2012). As mentioned above, AID are in general thought to act through a Th1-driven cell mediated immune response, while allergy and asthma involve a Th2-mediated response (Kreiner *et al.*, 2017). Type 1 responses, directed by Th1 $CD4^+$ T cells and identified by signature cytokine interferon (IFN)-ɣ, are considered as protective against infections by intracellular pathogens (O'Garra *et al.*, 2004) and have been implicated in the pathogenesis of AID, such as thyroid disease, rheumatoid arthritis, juvenile rheumatoid arthritis, insulin-dependent diabetes mellitus and multiple sclerosis (Romagnani, 1991). By contrast, type 2 responses, directed by Th2 $CD4^+$ T cells and identified by the signature cytokines interleukin (IL)-4, IL-5 and IL-13, are considered to play a pathogenic role in allergic diseases (Robinson, 2004). However, some observations have identified additional lymphocyte subsets, such as Th17 cells (Wynn, 2005), soluble factors such as IL-9 (Nowak *et al.*, 2010) and regulatory T cells (Bacchetta *et al.*, 2007) as a common link between atopy and autoimmunity. In fact, despite the reciprocal counter-regulation of Th1 and Th2 cells (Sornasse *et al.*, 1996) predicts that Th1-type AID and Th2-mediated allergic diseases would occur in mutually exclusive populations of patients, recent observations have challenged the validity of the long-standing Th1/Th2 paradigm (Steinman, 2007) and explain the immunological basis of cellular immune-mediated host defense and the pathogenesis of autoimmune and allergic diseases through a more complex hypothesis. As mentioned above, there is an increasing in the co-prevalence of autoimmune and allergic diseases. In addition, it also has been reported that infantile atopy increases a predisposition to autoimmune disorders, suggesting that these two entities might have common immune pathways, and justifying partially the increased co-prevalence of atopic and autoimmune diseases (Kokkonen *et al.*, 2004; Rabin *et al.*, 2008).

In what concerns the investigation of the pathophysiology of autoimmune and allergic diseases in the last five years, there is a lack of information and investigation. However, some papers give clues to the underlying pathophysiological mechanisms. In the study performed by Pedullá and collaborators, in addition to the increased prevalence of thyroid autoimmunity in children with atopic dermatitis, they also demonstrated that the frequency of thyroid autoimmunity was significantly higher among children with IgE-mediated than non-IgE-mediated atopic dermatitis, suggesting atopy and thyroid autoimmunity as potential outcomes of dysregulated immunity (Pedulla *et al.*, 2014). In line with this, Liphaus and collaborators demonstrated that juvenile systemic lupus erythematosus patients have increased IgE serum levels, an increase that was not related

to allergic or parasitic diseases. These results are in line with the hypothesis that high IgE levels can be considered a marker of immune dysregulation (Liphaus *et al.*, 2012).

In 2012, Lau and collaborators demonstrated that genetic deletion of STAT6, the key transcription factor for development of Th2 immunity, in lupus-prone Lyn-deficient mice, results in a profound skewing towards autoimmunity (classically described as a Th1-mediated immune response). In this work, they also demonstrated that STAT6 deficiency on a Lyn-deficient mice background suppresses spontaneous Th2 immunity in young mice but leads to early onset autoimmune disease and atopy in older mice (Lau *et al.*, 2012). It is of note that current therapies in the treatment of asthma are designed to target the Th2 pathway via inhibition of IL-4/13 or STAT6 signalling. On the discussion, the authors suggested that these types of strategies should now be viewed with caution, as they could lead to severe unwanted autoimmune responses or atopy in intrinsically susceptible individuals (Lau *et al.*, 2012).

Chai and collaborators performed a study to examine the production capacity of IL-10 and transforming growth factor β (TGF-β) 2 regulatory cytokines, in individuals with concomitant allergic rhinitis and Th1-type autoimmune diagnoses (type 1 diabetes mellitus, rheumatoid arthritis, Crohn disease, multiple sclerosis, thyroiditis (excluding Graves' disease), and Sjögren syndrome) and to compare that capacity with individuals with allergic rhinitis only and individuals with neither diagnosis. In this work, cases with allergic rhinitis and AID had significantly lower unstimulated IL-10 levels compared with controls with allergic rhinitis only, and significantly lower stimulated TGF-β levels compared with controls with neither diagnosis. Cases had consistently lower regulatory capacity compared with both control groups, as measured by an additive index using IL-10 and TGF-β levels. In this work, the authors concluded that individuals with concomitant allergic rhinitis and Th1-type autoimmune disorders have a lower regulatory cytokine production capacity than individuals with allergic rhinitis only and those with neither diagnosis (Chai *et al.*, 2005).

In consonance with this work, a later one appeared describing that autosomal recessive phosphoglucomutase (PGM) 3 mutations underlie a disorder of severe atopy, immune deficiency, autoimmunity, intellectual disability and hypomyelination. The results of this study showed that marked atopy and autoimmunity were associated with increased Th2 and Th17 cytokine production by $CD4^+$ T cells (Zhang *et al.*, 2014b). In addition, a prospective cohort study also suggested that Th1/Th2 hypothesis was too simplistic to explain the interaction between atopy and systemic onset juvenile idiopathic arthritis (SoJIA). In this work, Zhang and collaborators described that atopy may exert an adverse influence on SoJIA, as patients with atopy had a more active disease at diagnosis and

poorer outcome. In the results, at disease onset, 61 SoJIA patients were enrolled and were divided into SoJIA patients with atopy or those without atopy; atopic group at disease onset had significantly higher numbers of affected joints, ferritin levels and IgE serum levels than the non-atopic group; and, during the 2 years of follow-up time, the number of infections and the number of flares were significantly higher in the SoJIA with atopy group (Zhang *et al.*, 2014a).

Jung and collaborators performed a study with herpes virus entry mediator (HVEM), a newly discovered member of the tumour necrosis factor receptor (TNFR) superfamily that has a role in herpes simplex virus entry, in T cell activation and in tumour immunity. They generated monoclonal antibodies against HVEM and detected soluble HVEM in the sera of patients with various autoimmune diseases. HVEM was constitutively expressed on $CD4^+$ and $CD8^+$ T cells, $CD19^+$ B cells, $CD14^+$ monocytes, neutrophils and dendritic cells. In this work, the authors show that soluble HVEM levels were elevated in sera of patients with allergic asthma, atopic dermatitis and rheumatoid arthritis suggesting that the detection of soluble HVEMs might have diagnostic and prognostic value in certain immunological disorders (Jung *et al.*, 2003).

Also, in the previously referred study of Pacheco-Gonzalez, the authors showed that the genetic variants of FOXP3 that are more frequent in children who share allergic and AID, may alter the expression levels of FOXP3 modifying its function. In fact, FOXP3 gene is expressed mainly in a subgroup of $CD4^+$ cells, called regulatory cells (Treg) that represent 5-10% of $CD4^+$ T cells (Sakaguchi, 2005) and regulate the innate and adaptive immunity, thus contributing to the maintenance of immune tolerance (Rudensky, 2011; Sakaguchi, 2005). When their function is affected, autoimmune and allergic diseases can appear (Pacheco-Gonzalez *et al.*, 2016).

CONCLUSIONS

This review listed systematically the studies performed in the last fifteen years that establish an epidemiological, etiological or pathophysiological relationship between autoimmune and allergic diseases. In what concerns the epidemiology of both diseases, several works were published in the last years. Thus, although some authors reported results to the contrary, most studies point to an increase of co-prevalence of autoimmune and allergic diseases suggesting a relationship between them. Despite the increasing number of studies demonstrating this, there is some lack of information regarding the temporal relationship between the onset of one or the other disease. In fact, it would be interesting to know if both diseases co-exist or if, on the other hand, the existence of childhood allergies leads to the development of autoimmune diseases in adults (and vice versa).

Contrary to the results obtained regarding epidemiological data, in relation to the etiology and pathophysiology of the diseases, little has been added in the last fifteen years. In fact, only some authors described an overlap of genetic characteristics in autoimmune and allergic diseases. Although this information is important, it would be interesting to clarify common genetic mechanisms and relate them to the pathophysiology of the diseases. Commonalities in the genetic characteristics of both autoimmune and allergic diseases could provide a key to understand the complex relationship between them by pinpointing possible common pathophysiological mechanisms.

Based on the findings of this review, given the increasing evidence of a relationship between autoimmune and allergic diseases and the lack of knowledge in what concerns the overlap of their pathophysiologic mechanisms, future research should focus on identifying the basic mechanism of this relationship.

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